

1998.12.09 1998-208540(+1998US-208540) (2000.06.15) C07D
405/11, A61P 31/12, C07D 417/12, 213/15, 213/81

Novel thiourea derivatives useful for treating diseases associated with herpes viruses (Eng)

C2000-128176 N/AE AL AM AT AU AZ BA BB BG BR BY CA CH
CN CR CU C2 DE DK DM EE ES FI GB GD GE GH
GM HR HU ID IL IN IS JP KE KG KP KR KZ LK
LR LS LT LV MA MG MK MN MW MX NO
NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG UZ VN YU ZA ZW) R/AT BE CH CY DE
DK EA ES FI FR GB GH GM GR (IE IT KE LS LU MC
MW NL OA PT SD SE SL SZ TZ UG ZW)

Addnl. Data: BLOOM J D, DIGRANDI M J, DUSHIN R G, LANG S A,
O'HARA B M
1999.12.06 1999 WO-US28892

NOVELTY

Thiourea derivatives (I) are new.

REUTER

DETAILED DESCRIPTION

heterocycloalkyl, aryl or heteroaryl; or
 $R_7+R_8 = 3-7$ membered heterocycloalkyl;
 $A =$ heteroaryl;
 $W = Q$, NR_6 or is absent;
 $Y = CO$ or CO_2 or is absent;
 $Z = 1-6C$ alkyl, CN, CO_2R_6 , COR_6 , $CONR_6R_8$, $OCOR_6$, NR_6COR_6 ,
 $OCONR_6$, OR_6 , SR_6 , SOR_6 , SO_2R_6 , $SR_6NR_6R_8$ (sic), NR_6R_8 or
phenyl;
 $G =$ aryl or heteroaryl;
 $X =$ bond, NH, 1-6C alkyl, 2-6C alkenyl, 1-6C alkoxy, 1-6C thioalkyl,
1-6C alkylamino or CH;
 $J = 1-6C$ alkyl, 3-7C cycloalkyl, phenyl or benzyl; and
 $n = 1-6$.

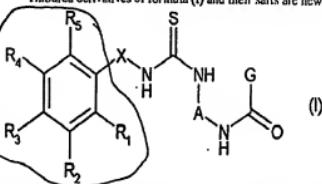
ACTIVITY

Virucide. In a V2V antiviral (ELISA) assay N-[2-(5-chloro-2,4-dimethoxy-phenyl)-thioureido]-pyridin-3-yl]-2-fluorobenzamide inhibited viral replication by 90% at a concentration of 10 micro g/ml.

USE

(I) are useful for inhibiting the replication of a herpes virus and treating herpes virus infections such as human cytomegalovirus,

Thiourea derivatives of formula (I) and their salts are new.



$R_1-R_3 = H$, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C perhaloalkyl,
3-10C cycloalkyl, 3-10C heterocycloalkyl, aryl, heteroaryl,
halo, CN, NO₂, COR₆, COR₆, OR₆, SR₆, SOR₆, SO₂R₆,
CONR₆R₈, NR₆R₈, NR₆R₈ or W-Y-CH₂-Z; or
R₆+R₇ or R₇+R₈ = 3-7 membered heterocycloalkyl or heteroaryl;
R₆, R₇ = H, 1-6C alkyl, 1-6C perhaloalkyl, 3-10C cycloalkyl, 3-10C

perhaloalkyl, 3-10C heterocycloalkyl or heteroaryl;

R₈ = H, 1-6C alkyl, 1-6C perhaloalkyl, 3-10C cycloalkyl, 3-10C

perhaloalkyl, 3-10C heterocycloalkyl or heteroaryl;

R₉ = H, 1-6C alkyl, 1-6C perhaloalkyl, 3-10C cycloalkyl, 3-10C

perhaloalkyl, 3-10C heterocycloalkyl or heteroaryl;

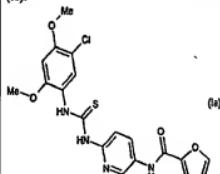
R₁₀ = W-O-

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herpes simplex virus, and varicella zoster virus (claimed). (I) are also useful for inhibiting and/or treating diseases associated with herpes viruses including Epstein-Barr virus, human herpes viruses-6 and -7, and Kaposi herpes virus.

SPECIFIC COMPOUNDS

31 Compounds (I) are claimed e.g. furan 2-carboxylic acid [6-[3-(5-chloro-2,4-dimethoxy-phenyl)-thioureido]-pyridin-3-yl]-amide (Ia).



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2000-423357/36

ADMINISTRATION

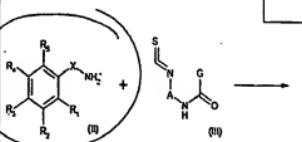
Dosage is 0.01-1000 mg/kg/day orally or 0.1-100 mg/kg/day parenterally.

EXAMPLE

To a solution of 2,5-dichloroaniline (0.16 g) in THF (20 ml) was added freshly prepared 1,1-thiocarbonylimidazole (0.2 g) and the mixture was stirred for 30 minutes at room temperature. [1,2,3]-Thiadiazole-4-carboxylic acid (4-amino- phenyl) amide (0.22 g) was added and the mixture was stirred for 6 hours. Work up gave [1,2,3]-thiadiazole-4-carboxylic acid [4-[3-(2,5-dichlorophenyl)-thioureido-phenyl]-amide.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) can be prepared by reacting appropriately substituted amines of formula (II) with appropriately substituted isothiocyanates of formula (III).



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